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(71) Applicant *(for all designated States except US)*: LUSOCHIMICA S.P.A. [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CASTELLI, Eugenio [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT). CASCIO, Giuseppe [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT). MANGHISI, Elso [IT/IT]; Via Giotto, 1, I-22050 Lomagna (IT).

(74) Agent: MINOJA, Fabrizio; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

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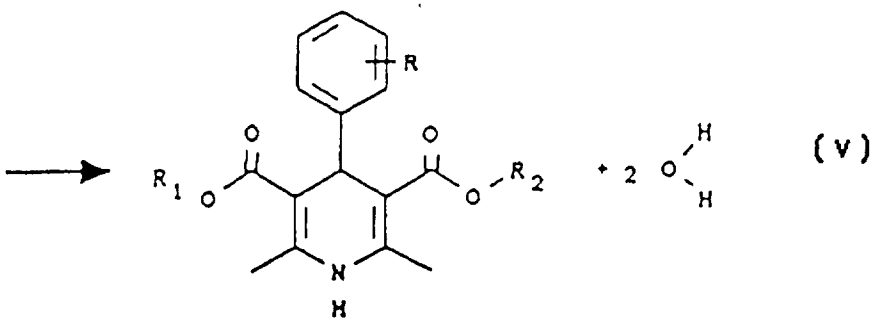
(54) Title: A PROCESS FOR THE PREPARATION OF DIHYDROPYRIDINES



(V)

(57) Abstract

A process for the preparation of dihydropyridines of formula (V) by Knoevenagel condensation of a benzaldehyde with an acetoacetic ester in the presence of β-alanine as a catalyst, and subsequent cyclocondensation of the resulting benzylidene acetoacetic ester with an amino crotonic ester.

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A PROCESS FOR THE PREPARATION OF DIHYDROPYRIDINES

The present invention relates to a novel process for the preparation of dihydropyridines.

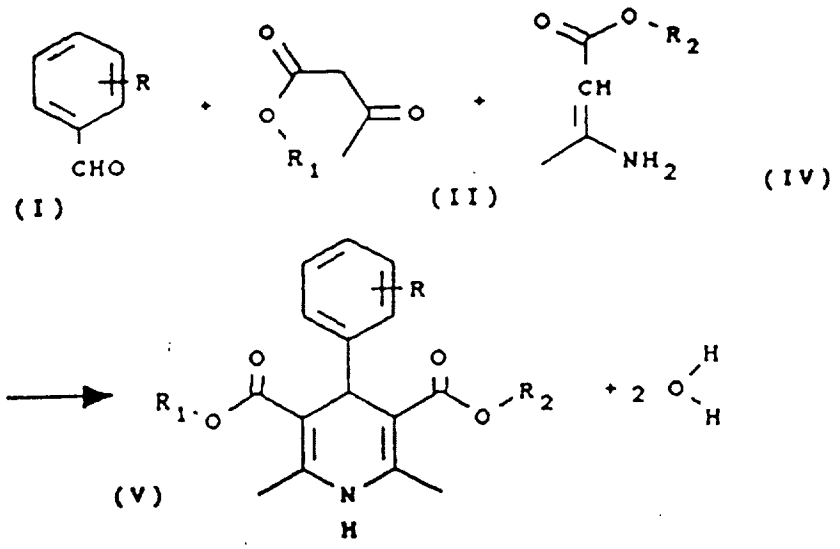
Prior art

A number of 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid (V) asymmetric diesters are well known active principles used in the treatment of cardiovascular conditions (see US 3932645, DE 2117573, US 4154839, DE 3222367, EP 7293).

Since these compounds started being prepared on an industrial scale, enormous efforts were directed in the experimental field to improve the yield and the purity of the final product.

In fact, when said compounds are prepared by means of a single step Hantzsch synthesis (scheme 1) undesired by-products usually form, the removal of which is difficult, expensive and often requires an environmentally complex work-up (see EP 124743 and EP 534520).

Scheme 1

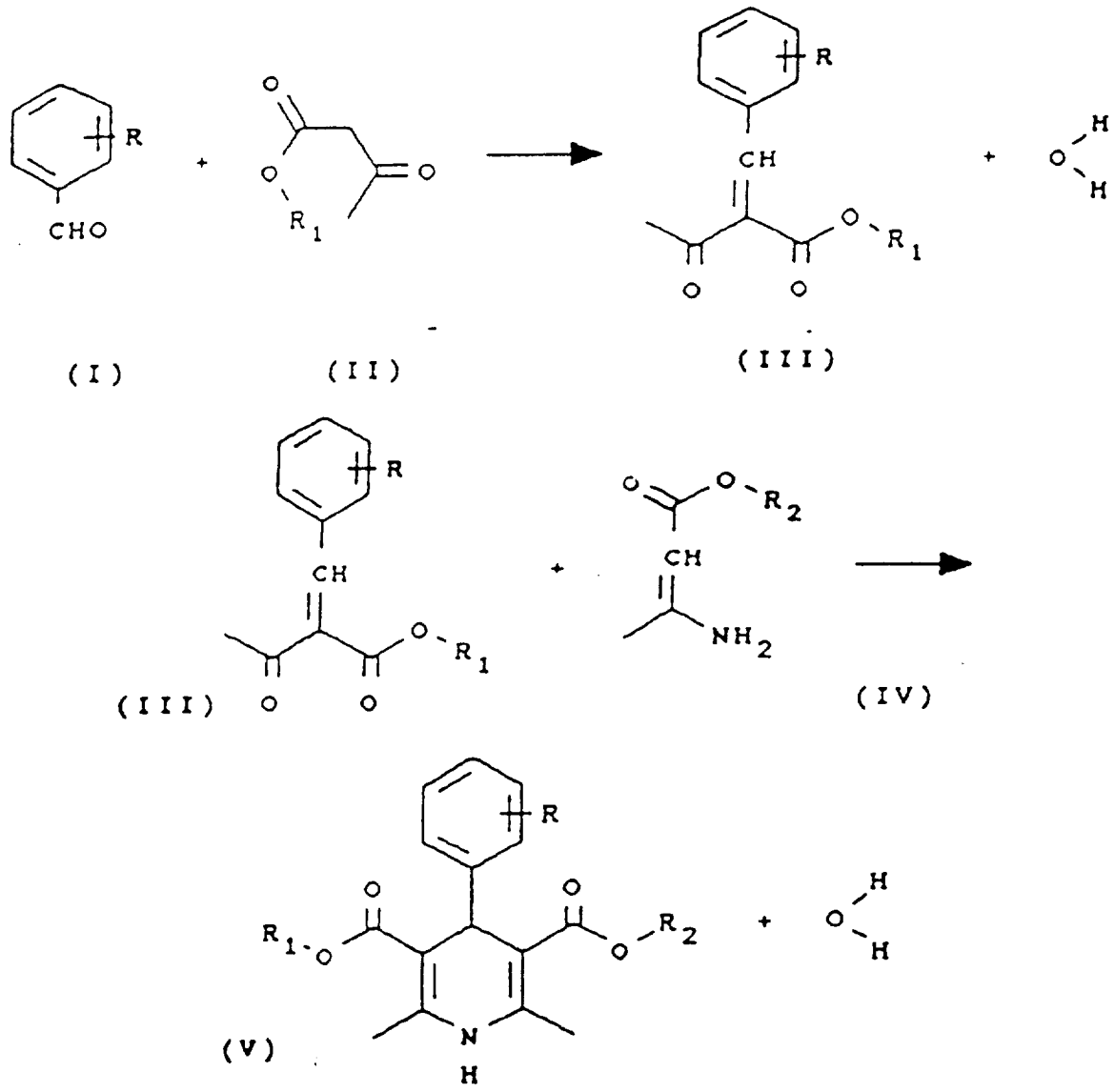


As it is well known to those skilled in the art, in organic chemical synthesis, in order to obtain highly pure products, the formation of by-products should be avoided instead of improving the purification of a crude mixture.

The prior art (EP 124743, EP 319814, EP 534520), in order to reduce the formation of by-products, suggests a two-step synthesis, i.e. a Knoevenagel condensation of a benzaldehyde (I) with an acetoacetic ester (II) to give a benzylidene acetoacetic ester (III), followed by a cyclocondensation of said benzylidene acetoacetic ester (III) with a 3-amino crotonic ester (IV), (scheme 2).

This general approach proves to be particularly important in the preparation of those compounds in which the two ester functions are not very different from each other, such as those listed in scheme 2:

Scheme 2



wherein R, R_1 and R_2 are:

a) R=2, 3-Cl_2, R_1=CH_3 or C_2H_5, R_2=CH_3 or C_2H_5 and R_1 is different from R_2 (V=Felodipine);

b) R=3-NO_2, R_1=CH_3 or C_2H_5, R_2=CH_3 or C_2H_5 and R_1 is different from R_2 (V=Nitrendipine);

c) R=3-NO_2, R_1=$CH(CH_3)_2$ or $CH_2CH_2OCH_3$, R_2=$CH(CH_3)_2$ or $CH_2CH_2OCH_3$ and R_1 is different from R_2 (V=Nimodipine);

d) R=2-NO_2, R_1=CH_3 or $CH_2CH(CH_3)_2$, R_2=CH_3 or $CH_2CH(CH_3)_2$ and R_1 is different from R_2

(V=Nisoldipine).

The preparation of Felodipine, for example, has been described according both to a single-step synthesis (EP 7293, ES 537424), and to a two-step one (EP 7293, EP 124743, ES 549753, ES 536229, EP 534520), according to schemes 1 or 2.

Again in field of similar Hantzsch synthesis, starting from more complex raw materials, products have been prepared having functional groups or substituents which can subsequently be removed, which made the purification of the product easier (EP 95451, EP 95450). However, these processes suffer from even greater problems in terms of operations, costs and environmental hazards.

EP 124743 discloses the synthesis of benzylidene intermediates of high purity, in order to avoid the formation of by-products in the second step, starting from ordinary raw materials (appropriate benzaldehyde and acetoacetic esters), in a low molecular alcohol as the solvent, and with piperidine acetate as the catalyst. The main drawback of this synthesis resides actually in the use of a catalyst prepared starting from acetic acid and piperidine, which products obviously involve handling problems due to their characteristics of toxicity, corrosivity and inflammability.

JP 78 53638 (CA 89:179714) also discloses, although not in connection with dihydropyridines synthesis, similar reaction conditions in the synthesis of benzylidene acetoacetic esters.

EP 534520 describes the inhibition of the formation of by-products during the cyclocondensation (second

step, scheme 2), by means of a short thermal reaction between a benzylidene acetoacetic ester and an amino crotonic ester in a water-miscible solvent (preferably a low molecular alcohol), combined with, or followed by, the addition of a strong acid to the reaction mixture. It is evident that the addition of acid is a source of drawbacks to the industrial production, such as a limitation in the use of reactors, containers or steel apparatuses, an increase in the operative risks and the like. Moreover, being it the last step in the preparation of a pharmaceutical active ingredient, additional washing procedures have to be applied to ensure the final product is free from acids.

Object of the present invention

The present invention avoids the formation of by-products in the Hantzsch synthesis of dihydropyridines (in two steps), thanks to a process which makes use of:

a) less expensive and less environmentally risky conditions in the Knoevenagel condensation (first step, scheme 2), which allow to obtain extremely pure intermediate benzylidene acetoacetic esters in a good yield;

b) mild reaction conditions (anyhow inhibiting any side-reactions) in the second step (scheme 2), which allow to obtain an extremely pure final product in a high yield, by means of a very simple work up.

The process of the invention is carried out in an alcohol medium, at temperatures from 20°C to 60°C, in the presence of β-alanine (3-aminopropanoic acid) as the catalyst.

A number of different catalysts are described in

literature for the Knoevenagel condensation (Organic Reactions, vol. 15, chapter 2); among these, amino acids (see for example J. Biol. Chem. 1909, page 49; J. Chem. Soc. 1951, page 3155) have extensively been studied. The Applicant carried out a series of experiments with amino acids as possible catalysts, many of them proving to be ineffective (for example piperidine-4-carboxylic acid, phenylalanine, glycine). On the contrary, β-alanine (3-aminopropanoic acid) turned out to be a very interesting, effective catalyst which allows to prepare highly pure intermediates in quite satisfactory yields.

Moreover, β-alanine exerts its catalytic activity in rather low catalyst/aldehyde molar ratios (3%), thus permitting, for example in the preparation of Felodipine intermediate, a β-alanine/2,3-dichlorobenzaldehyde 1.5% weight ratio, compared with a piperidine acetate/2,3-dichlorobenzaldehyde 5.2% weight ratio stated in example 3 of EP 124743.

Assuming approximately the same cost for β-alanine and piperidine acetate, the use of the former instead of the second involves a 70% decrease in the catalyst cost.

β-Alanine is also preferable to piperidine acetate for environmental reasons, and it also involves the remarkable advantage of replacing two toxic potential impurities (acetic acid and piperidine) of the final dihydropyridine product with only one ordinary potential impurity (β-alanine), as it turns out from the comparison between the data inferable from the Registry of Toxic Effects of Chemical Substances (for the definitions of toxic and ordinary impurities see USP XIII, page 1922).

The mild reaction conditions of the process of the invention have been selected on the ground of the surprising observation that the formation of by-products is highly inhibited when the above mentioned cyclocondensations (scheme 2) are carried out in a solvent mixture consisting of a water-immiscible solvent (preferably toluene) and a protic organic solvent (preferably a low molecular alcohol) in a volume ratio ranging from 80% water-immiscible solvent - 20% protic solvent to 95% water-immiscible solvent - 5% protic solvent, at a reaction temperature from 80°C to 145°C, in reflux conditions with separation of water.

Following this process, the cyclocondensation can be thermally completed drastically reducing the formation of by-products: the total amount of the two symmetrical esters (formula V with $R_1=R_2$) is lower than 0.1% in the final product.

The reaction is slower when the cyclocondensation is effected in pure toluene, although the formation of by-products is inhibited. On the other hand, as stressed in EP 534520, when the same reagents are refluxed in a pure protic solvent such as ethanol until completion of the cyclocondensation, undesired by-products can form in unacceptable amounts if no strong acids are added to the mixture, with the above mentioned drawbacks.

The process of the present invention, being free from risks of formation of by-products, advantageously yields a final dihydropyridine product of high purity, moreover allowing very simple, versatile reaction conditions, which are also advantageous from the environment and costs point of views.

The following example further illustrates the process of the invention.

Example

1) Methyl 2-[(2,3-dichlorophenyl)methylene]-3-oxobutanoate (IIIa) (methyl 2,3-dichlorobenzylidene acetoacetate, intermediate in the synthesis of Felodipine):

350 g (2 mol) of 2,3-dichlorobenzaldehyde (Ia), 600 ml of isopropyl alcohol and 232.6 g (2 mol) of methyl acetoacetate (IIa) are mixed at a temperature of 25°C, with stirring and under nitrogen atmosphere. The mixture is heated to a temperature from 50°C to 55°C, to obtain a clear solution in a few minutes.

After that, 5 g (0,056 mol) of β-alanine dissolved in 100 ml of deionized water are added, keeping temperature between 50°C and 60°C for one hour.

The mixture is then slowly cooled to room temperature (20°-25°C), again with stirring and under nitrogen atmosphere, keeping these conditions for 12 hours. The reaction product precipitates (optionally by seeding with some methyl 2,3-dichlorobenzylidene acetoacetate crystals), the mixture is cooled at 0°C and left at this temperature for at least 3 hours.

Afterwards the mixture is filtered through a sintered glass funnel , the solid is washed with 100 ml of cold isopropyl alcohol (0°C) and recrystallized in 500 ml of isopropyl alcohol.

After pressing and drying under vacuum (6 hours, 50°C) the desired compound is obtained as a crystalline white powder (391 g; 1,43 mol; yield: 71%), with m.p.= 81.5°-82.5°C, which is identified by ^{1}H-NMR spectrum

(FT-200MHz, $CDCl_3$, δ ppm: 7.78 (s 1H); 7.44 (d 1H); 7.24 (d 1H); 7.18 (q 1H); 3.67 (s 3H); 2.42 (s 3H); and analyzed by quantitative TLC (stat. phase: F 254 Merck; mobile phase: AcOEt/hexane 1/4): 2,3-dichlorobenzaldehyde content lower than 0.01%.

2) 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedi-carboxylic acid ethyl, methyl ester (Va) (Felodipine):

185 g (1.43 mol) of ethyl 3-aminocrotonate (IVa) and 391 g (1.43 mol) of methyl 2,3-dichlorobenzylidene acetoacetate (IIIa) are dissolved in 1000 ml of solvent, consisting of 800 ml of toluene and 200 ml of isopropyl alcohol, in a 2 litre round bottom flask, fitted with a Marcusson condenser, with stirring, under nitrogen atmosphere and shielded from direct light. The mixture is heated to reflux (T = about 100°C), observing almost immediately the separation of water in the Marcusson condenser. The solvent is refluxed for 8-12 hours, then the mixture is slowly cooled to room temperature (20°-25°C), with stirring. After about 12 hours, the mixture contains the solid reaction product (as in the above example, in case of a supersaturated solution, seed crystals can be made use of).

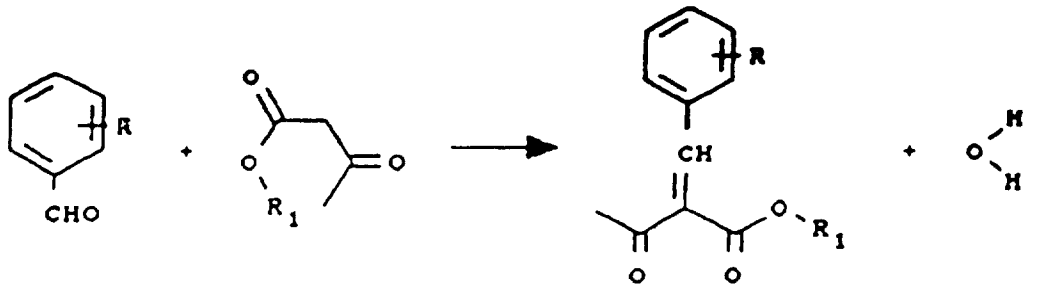
The mixture is cooled to 0°C stirring at this temperature for at least 3 hours, then filtered through a sintered glass funnel, washing first with 80 ml of cold toluene (0°C), then with 200 ml of cold hexane (0°C). The solid is pressed thoroughly on the funnel, then dried under vacuum (8-12 hours, 50°C), to obtain 499 g of the desired product (1.3 mol, yield: 91%.) as a pale yellow crystalline powder with m.p. = 145°C, which

is identified by ^{1}H-NMR spectrum (FT-200MHz, $CDCl_3$ δ ppm: 6.90-7.30 (mult. 3H); 6.53 (s 1H); 5.44 (s 1H); 4.02 (q 2H); 3.58 (s 3H); 2.21 (2s superimp. 6H); 1.15 (t 3H) and analyzed by HPLC (stat. phase: RP-18 Lichrosorb Merck, mobile phase: acetonitrile/water 1/1): felodipine: 99.8% (area); dimethyl ester: 0.07% (area); diethyl ester: 0.02% (area).

CLAIMS

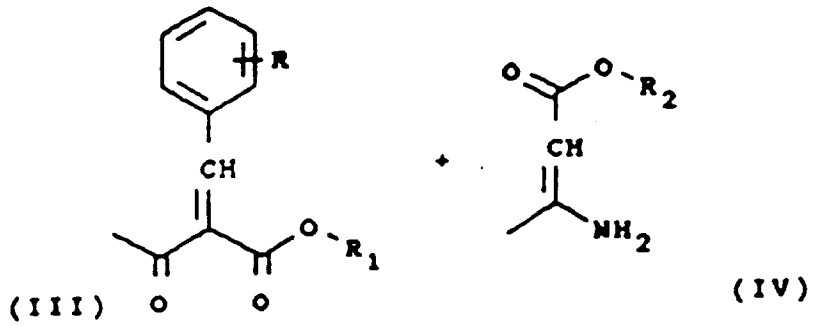
1. A process for the preparation of dihydropyridines of formula (V), comprising the following steps:

1) Knoevenagel condensation of a benzaldehyde (I) with an acetoacetic ester (II) to give a benzylidene acetoacetic ester (III):



(I) (II) (III)

2) cyclocondensation of (III) with an amino crotonic ester (IV):



(III) (IV)

wherein R, R_1 and R_2 are:

a) R=2, 3-Cl_2, R_1=CH_3 or C_2H_5, R_2=CH_3 or C_2H_5 and R_1 is different from R_2;

b) R=3-NO_2, R_1=CH_3 or C_2H_5, R_2=CH_3 or C_2H_5 and R_1 is different from R_2;

c) R=3-NO_2, R_1=$CH(CH_3)_2$ or $CH_2CH_2OCH_3$, R_2=$CH(CH_3)_2$ or $CH_2CH_2OCH_3$ and R_1 is different from R_2;

d) R=2-NO_2, R_1=CH_3 or $CH_2CH(CH_3)_2$, R_2=CH_3 or $CH_2CH(CH_3)_2$ and R_1 is different from R_2;

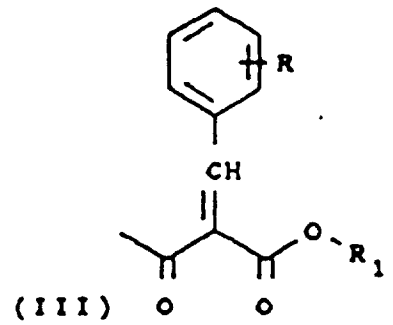
characterized in that the first step is carried out in the presence of β-alanine as the catalyst, in a low molecular aliphatic alcohol solvent, at a reaction temperature ranging from 20°C to 60°C; and in that the second step is effected in a solvent consisting of a mixture of a water-immiscible organic solvent and a low molecular aliphatic alcohol, at a reaction temperature from 80°C to 145°C.

2. A process according to claim 1, in which, in the first step, the molar ratio β-alanine catalyst to compound (I) is comprised from 1% to 10%.

3. A process according to claim 1, in which, in the second step, the water-immiscible organic solvent has a boiling point, under one atmosphere pressure, not lower than 80°C.

4. A process according to claim 1, in which, in the second step, the solvent mixture volume ratio ranges from 80% water-immiscible solvent - 20% alcohol to 95% water-immiscible solvent - 5% alcohol.

5. A process for the preparation of benzylidene acetoacetic esters of formula (III)



(III)

in which a benzaldehyde (I) and an acetoacetic ester

(II) are subjected to a Knoevenagel condensation, which process is carried out in the presence of β-alanine as the catalyst, in a low molecular aliphatic alcohol solvent, at a reaction temperature ranging from 20°C to 60°C.

6. A process according to claim 5, in which the molar ratio β-alanine catalyst to compound (I) ranges from 1% to 10%.

INTERNATIONAL SEARCH REPORT

Interl. ,nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 534 520 A (MERCK & CO INC) 31 March 1993 cited in the application see page 9, line 33 - line 55; claim 1	1-6
X	EP 0 319 814 A (BAYER AG) 14 June 1989 see page 6; claim 10	1-6
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X	EP 0 100 189 A (PFIZER LTD ;PFIZER (PA)) 8 February 1984 see page 25; claim 6	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 088 276 A (BAYER AG) 14 September 1983 cited in the application see claim 6	1-6
X	EP 0 007 293 A (HAESSLE AB) 23 January 1980 cited in the application see claim 5	1-6
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